REMARKS

The Office Action and cited and applied references have been carefully reviewed. No claim is allowed. Claims 1, 3, 5, 11, 12, 15, 16, 18, 19, 21, 22, 29, 30, 32, 33, 40, 41, 43, 47, 52, 56 (claim 58 renumbered by the examiner) and 57 (claim 59 renumbered by the examiner) presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

The examiner states that non-patent literature documents cited at page 2 of the Information Disclosure Statement filed September 12, 2007, have not been considered because the citations are incomplete inasmuch as the titles of the journals have been omitted. A new PTO SB08a form listing those same non-patent literature documents (and identifying their journal titles) and newly cited references is submitted herewith in an IDS, along with copies of all references listed thereon, for consideration by the examiner.

The examiner acknowledged applicants' claim under 35 U.S.C. §§ 119(e) and/or 120, 121, or 365(c) for benefit of the earlier filing date of PCT/IL03/00501, filed June 12, 2003, which claims benefit of provisional application no. 60/388,273, filed June 12, 2002. However, the examiner is of the opinion that claims 1, 3, 5, 11-44, 47-53, 56, and 57 do not properly benefit under §§ 119 and/or 120 from the earlier filing dates of the

priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure. The examiner asserts that the claims do not properly benefit from the earlier filing date of provisional application no. 60/388,273 since that application fails to provide written support for the language of the claims. The examiner then contends that, without limitation, but as an example, it is noted that claim 1 is drawn to a polynucleotide encoding a fusion polypeptide comprising an antigenic peptide from a pathogen, which is either fungal or parasitic in origin; yet, the provisional application does not appear to provide support for such a claim. As another example, the examiner indicates that claim 1 is drawn to a polynucleotide encoding a fusion polypeptide comprising the full or partial transmembrane and/or cytoplasmic domains of CD40; yet, it appears to the examiner that the provisional application does not disclose such a fusion polypeptide and thus fails to provide written support for such a claim.

Applicants disagree with the examiner that there is lack of adequate written description and a sufficiently enabling disclosure for the reasons discussed below for the 35 U.S.C. §112, first paragraph, rejections. Thus, applicants still claim priority from provisional application no. 60/388,273, filed June 12, 2002, for claims 1,3,5, 11-44,47-53, 56, and 57. However,

regarding the subject matter of a polynucleotide encoding a fusion polypeptide comprising an antigenic peptide from a pathogen, which is either fungal or parasitic in origin and a fusion polypeptide comprising the full or partial transmembrane and/or cytoplasmic domains of CD40, applicants concede that the effective filing date of the claims directed to this particular feature is the filing date of international application PCT/IL03/00501, namely June 12, 2003.

The specification has been objected to because the claims are directed to a plurality of tumor-associated antigens (TAA), which the specification expressly discloses includes "any TAA peptide known or to be discovered in the future as periodically published in Cancer Immunity, a Journal of the Academy of Cancer Immunology, at the website www.cancerimmunity.org/ peptidedatabase/Tcellepitopes.htm. (paragraph [0079] of the published application). The examiner has objected to this reference.

Applicants' intent was to emphasize the fact that the list of TAAs provided is for the purpose of example only and should not be construed to limit the invention in any way. Since the list of TAAs provided in the specification on pages 15-17 are presented as being representative but non-limiting examples of TAAs, the specific embodiments of the generic TAA recited as a component in the polynucleotide construct are considered to be

non-essential material. Applicants' intent may be expressed without specifically referring to the website or mentioning TAAs to be discovered in the future and, while the disclosure objected to by the examiner should be considered non-essential material, this objection is obviated by amendment to page 18 of the specification deleting this disclosure to non-essential material.

Reconsideration and withdrawal of this objection are therefore respectfully requested.

Claims 1, 11, 32, 38, 39, 47, 48, 56, and 57 have been objected to because of the repeated use of the terms "carboxyl terminal" and "amino terminal" instead of "carboxyl terminus" and "amino terminus". This objection is obviated by the amendments to the claims.

Reconsideration and withdrawal of this objection are therefore respectfully requested.

Claims 16, 17, 20, 35 and 36 have been separately objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claim 16 has been amended in accordance with the examiner's suggestion to depend from claim 12 (claim 14 is cancelled), as opposed to being dependent from claim 15, thereby obviating this part of the objection.

The examiner states that claim 17 depends from claim 14, which in turn depends from claim 12; yet, the limitation recited by both claims 12 and 17 is the same. This part of the objection is obviated by the cancellation of claim 17 without prejudice and by the amendment of claim 18 to be ultimately dependent from claim 12 instead of claim 17.

The examiner states that claim 20 depends from claim 14, which in turn depends from claim 12. According to claim 12, the at least one antigenic peptide is at least one antigenic determinant of one sole antigen. As such, the examiner holds that the at least one antigen peptide, as in accordance with claim 20, cannot also be at least one antigenic determinant of each of at least two different antigens. This part of the objection is obviated by the cancellation of claim 20 without prejudice. Also, the features of claim 13 has been incorporated as an alternative in claim 12, and claim 21 has been amended to depend from claim 12 instead of from claim 20.

The examiner states that claim 35 should be amended to depend from claim 32 rather than from claim 34, because if the antigenic peptide is at least one peptide derived from at least one TAA, it is not a peptide comprising a MHC class I epitope of an antigen from a pathogen or at least one idiotypic peptide (rather it is a peptide comprising a MHC class I epitope of a TAA). This part of the objection is obviated by amending claim

35 to depend from claim 32, with claim 34 being cancelled without prejudice.

The examiner states that claim 36 should be amended to depend from claim 32 rather than from claim 34, because if the antigenic peptide is at least one peptide derived from an antigen from a pathogen, it is not a peptide comprising a MHC class I epitope of an antigen from a TAA or at least one idiotypic peptide (rather it is a peptide comprising a MHC class I epitope of an antigen from a pathogen). This part of the objection is made moot by the cancellation of claim 36 without prejudice.

Finally, the examiner states that the claims (e.g., claim 1) are objected to because of the use of the term "sequence", apparently with intent to denote a peptide or polypeptide. While applicants do not necessarily agree with the examiner's position regarding the usage of the term "sequence", this part of the objection is made moot by the amendment to the claims to replace the term "sequence" where appropriate with the term "polypeptide".

Reconsideration and withdrawal of the objections are therefore respectfully requested.

Claims 1, 3, 5, 11-44, 47-53, 56, and 57 have been rejected under 35 U.S.C. §101 because the examiner states that the claimed invention is not supported by either a specific and

substantial asserted utility or a well-established utility. This rejection is respectfully traversed.

The examiner explains that the considerations that are made in determining whether a claimed invention is supported by either a specific and substantial asserted utility or a well-established utility are outlined by the published Utility Examination Guidelines (Federal Register; Vol. 66, No.4, January 5, 2001). According to the examiner, a "specific and substantial" asserted utility is an asserted utility that is specific to the particular nature and substance of the claimed subject matter, and which would be immediately available for application in a "real-world" context by virtue of the existing information disclosed in the specification and/or on the basis of knowledge imparted by the prior art, such that its use would not require or constitute carrying out further research to identify or reasonably confirm its usefulness in this context. A "well established" utility is a credible, specific, and substantial utility, which is well known, immediately apparent, and implied by the specification, and based on the disclosure of the properties of a material or subject matter, either alone or taken with the knowledge of one skilled in the art.

The examiner states that each of the inventions as claimed in claims 1, 3, 5, 11-44, 47-53, 56, and 57 is disclosed as useful to prevent or treat cancer or infectious diseases in a

mammal. Yet, the examiner alleges that "to employ the claimed inventions in the prevention or treatment of cancer and any of a plurality of infectious diseases, as is the asserted utility of the claimed invention, would clearly require further research, which should be regarded as constituting part of the inventive process. Moreover, the existing information disclosed by applicants' application would merely provide the artisan with an invitation to perform such investigations, which might ultimately lead to a derivation of a specific benefit, or which might not; and in either case, an immediate benefit could not be derived from the use of the claimed invention because the existing information is insufficient to enable the artisan to use the claimed polynucleotide in the manner asserted to provide an immediate benefit." The examiner cites a decision of the court stating: "[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." Brenner, Comr. Pats. v. Manson, 148 U.S.P.O. 689 at 696 (US SupCt, 1966). The examiner is therefore of the opinion that "because the specification does not disclose a currently available, "real world" use for the claimed inventions, the requirements set forth under 35 U.S.C. § 101 have not been met."

The examiner states that the utility of the invention may be to treat or prevent an infectious disease, but the polypeptide of the invention may comprise a tumor-associated

antigen. Therefore, it is apparent that the claimed invention cannot be regarded as practically useful in the "real-world" setting of the clinic or hospital since, for example, a vaccine comprising a fusion polypeptide comprising an antigen associated with a bacterium is not reasonably expected to stimulate an immune response in a mammal that is effective to prevent or treat cancer in the mammal. The examiner also provides a mirror-image example where a vaccine comprising a fusion polypeptide comprising a tumor-associated antigen is not reasonably expected to stimulate an immune response in a mammal that is effective to prevent or treat an infectious disease. Thus, the examiner submits that the assertion that the claimed inventions are useful in some abstract capacity to prevent or treat some unspecified type of cancer or infectious disease, where the claimed product would ordinarily not be considered so useful, lacks the necessary specificity and substantiality of an asserted utility in the chemical arts that might otherwise fulfill the requirements of 35 USC §101.

While applicants completely disagree with the examiner's position above that the claimed invention cannot be regarded as practically useful in the "real world" setting of a clinic or hospital because the examiner is constructing the presently claimed invention in a manner that is diametrically opposed to how it would be construed by those of skill in the

art, this particular issue is nevertheless obviated, purely for purposes of business strategy considerations and without prejudice, by the cancellation of claims 14, 23-27, 34, 36 and 42 and by the amendment of claims 1 and 32 to recite that the "at least one antigenic peptide comprising an MHC class I epitope" is tumor-associated antigen (TAA). Accordingly, it can no longer be alleged that the presently claimed invention cannot be regarded as practically useful in the "real world" setting of the clinic or hospital.

The examiner then continues with a discussion of "the assertion that the claimed inventions are useful to prevent or treat any given type of cancer." The examiner states that "… the prevention of cancer, a disease affecting so many different types of cells, tissues, and/or organs, is an intractable proposition, if not now wholly impractical, given, for example, that it is such a heterogeneous disease, having widely varying pathologies and etiologies, and that its causes are multifactorial and as yet only partially characterized and poorly understood. It is generally recognized that a disease cannot be prevented unless and until its causes are fully appreciated and understood to a degree that it becomes possible to intercede effectively to block its onset or development. As such, the information contained in the specification, which too inadequately describes the claimed inventions that are useful for preventing any of the large

plurality of such disparate types of cancer, would not be sufficient to permit their immediate use by the skilled artisan in the intended manner to prevent any specific type of cancer in the mammal treated using the inventions."

While applicants respectfully disagree with the examiner, nevertheless, only for the sake of advancing prosecution, applicants have deleted the term "prevention" from claim 43 without prejudice. This has been done in spite of the fact that evidence has previously been presented in the 1.132 declaration filed on November 29, 2007, and again re-submitted on August 11, 2008, and April 15, 2009, demonstrating that the growth of tumors in mice can be prevented by prior vaccination with the cellular vaccine of the invention. Applicants wish to point out that it is not true that "a disease cannot be prevented unless and until its causes are fully appreciated and understood to a degree that it becomes possible to intercede effectively to block its onset or development." Certainly, diseases like polio or any other disease against which effective vaccines exist are not all fully appreciated and understood and yet can be prevented. Since this part of the rejection as it relates to "prevention" is obviated by the amendment to delete the recitation of "prevention" without prejudice, and furthermore, in order to simplify applicants' response, applicants will focus on the aspect of treating, not preventing, cancer.

Starting on page 16, last paragraph, the examiner relates to the issue of the therapeutic vaccine intended for use in treating (not preventing) cancer. The examiner alleges that "while many cancer vaccines have been placed in clinical trials, the results thus far have been disappointing and even discouraging and takes the position that it has become evident that simply stimulating an immune response against a given antigen that is associated with a particular type of cancer, for example, is more often than not ineffective to treat the disease.

Applicants respectfully disagree with the examiner for the following reasons:

1. Provenge (Sipuleucel-T), an immunotherapy product designed to stimulate T-cell immunity against prostatic acid phosphatase has been extensively tested in the clinical setting (see the Small et al., *J Clin Oncol* 24:3089-3094 reference; and the abstract, Drugs RD 2006 Sipuleucel-T, submitted herewith in an IDS) and was approved by the FDA on April 29, 2010, for use in the treatment of advanced prostate cancer patients. The drug is protected by five different US patents (7,414,108; 6,210,662; 6,194,152; 6,080,409; 5,976,546), one of which (US 6,080,409) is directed to "[a] method of inducing a T cell-mediated cellular immune response to a soluble peptide antigen in a mammalian subject…" In the dependent claims, the method of claim 1 is claimed for use in treating prostate and breast cancer, wherein

the soluble antigen is prostatic acid phosphatase (PAP) or Her-2, respectively. In the description, experimental support is disclosed only for the antigen prostatic acid phosphatase (PAP, although support for Her-2 was provided later in an affidavit), certainly not for the full scope of the claimed invention. It should also be noted here that the phase III clinical trial which led to the approval of the drug (Small et al, *supra*) found that patients treated with Provenge lived an average of 4.1 months longer than patients treated with the control (autologous cells without the GM-CSF / PAP fusion protein). Thus, even though the benefits of Provenge are marginal, the USPTO found there is utility for the five patents issued for this cancer vaccine.

2. The USPTO has determined in many instances that the treatment of cancer is legitimate utility for a cancer vaccine. A search for patents having claims directed to cancer vaccines came up with 22 US patents with such claims. One example is US 7,718,762, issued May 18, 2010, which claims "A composition comprising a plurality of oncofetal antigen (OFA) epitopes that specifically stimulate T cytotoxic lymphocytes in a mammal, and a carrier, wherein said composition does not comprise any OFA epitope that specifically stimulates T suppressor cells." Claim 23 in this patent is directed to "A method of treating cancer in a mammal, comprising administering to a mammalian cancer patient the composition of claim 1. The study disclosed in the

specification of this patent reveals a number of specific antigenic determinants as described in Table 2 (column 29). Nevertheless, claim 1 defines oncofetal antigens in general and they have not been restricted to those shown to be antigenic in the examples. Furthermore, no examples show the efficacy of the oncofetal antigens even in *in vitro* settings; only a prophetic example for determination of OFA/iLRP epitopes for use in humans is disclosed.

3. In the examiner's comments, the examiner cites literature published 10-16 years ago, to show that cancer cannot be treated with cancer vaccines. This issue is discussed in the present specification at page 4, second full paragraph (paragraph [0010] in published patent application US 2006/0003315):

> Indeed, some encouraging data showing CTL induction and vaccine efficacy came from animal studies exploring either type of above-described approaches. However, clinical success in human trials has so far been limited, with little correlation between the observed number of specific anti-tumor CTLs and the actual clinical response (Sogn, 1998; Moingeon, 2001; Jager et al., 2002). This is attributed, in part, to requirement for help from CD4+ cells and to immunosuppressing cytokines produced by the tumor cells, but also to the fact that many of the identified MHC class I-associated TAA peptides are poorly presented on the cell surface because of low level of protein expression and low affinity for their restricting MHC class I molecule.

In paragraph [0012] of US'315, which corresponds to the first full paragraph on page 5 of the present specification, it is stated that:

> A single cell can display thousands of different MHC class I bound peptides, most of them only at low frequency of less than 0.1% of the total. The density of MHC/peptide complexes on the cell surface determines the degree of T cell responsiveness (Levitsky et al., 1996; Tsomides et al., 1994; Gervois et al., 1996). CTL priming by a professional APC generally requires a higher density of specific complexes than that required on the surface of the target cell for activation of an armed effector CTL (Armstrong et al., 1998; Reis e Souza, 2001). The ability to generate high numbers of particular MHC class I/peptide complexes on the APC itself could, therefore, be of great value. (emphasis added)

Attempts to obtain such an ability have been made by others (see paragraph [0013], which corresponds to the paragraph bridging pages 5 and 6 of the present specification), but the present invention is the first to provide increased peptide presentation on APCs (see for example the disclosure in paragraph [0033], corresponding to the second full paragraph on page 11 of the present specification). Since the present specification clearly shows that the invention provides a significant advantage over existing technologies, the failures of past attempts using the old technology cannot stand as evidence for the intractability of the treatment of cancer with cancer vaccines.

MPEP 2107.01 II on "Wholly Inoperative Invention; Incredible Utility" cites case law and states as follows:

> However, as the Federal Circuit has stated, "[t]o violate [35 U.S.C.] 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401, 1412 (Fed. Cir. 1992) (emphasis added). See also *E.I. du Pont De Nemours and Co. v. Berkley and Co.*, 620 F.2d 1247, 1260 n.17, 205 USPQ 1, 10 n.17 (8th Cir. 1980) ("A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, the defense of non-utility cannot be sustained without proof of total incapacity." If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. See *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); *In re Gardner*, 475 F.2d 1389, 177 USPQ 396 (CCPA), *reh'g denied*, 480 F.2d 879 (CCPA 1973); *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).
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> Situations where an invention is found to be "inoperative" and therefore lacking in utility are rare, and rejections maintained solely on this ground by a Federal court even rarer. In many of these cases, the utility asserted by the applicant was thought to be "incredible in the light of the knowledge of the art, or factually misleading" when initially considered by the Office. *In re*

Citron, 325 F.2d 248, 253, 139 USPQ 516, 520 (CCPA 1963).

As would be instantly appreciated and understood by those of ordinary skill in the art, whose level of skill is high in the relevant art, reading the present specification, e.g., the third paragraph on page 2, the tumor-associated antigens (TAA) are used to specifically activate CTLs against a particular antigen (TAA) so as to be capable of killing the cell that contains or expresses the antigen. Accordingly, those of skill in the art would fully understand and recognize that the presentation of the antigenic peptide comprising an MHC class I epitope that is a TAA is used to treat a cancer for which the cancer cells expresses the TAA, and NOT any arbitrary cancer cell or a cell infected with a pathogen. This is clearly a credible utility.

Further relating to citation of the relevant art, applicants would like to point out that the art of cancer vaccine is rapidly evolving and great advances have been made during the last 16 years, leading to many developments in addition to Provenge discussed above. Several excellent recent papers, (copies of which are being submitted herewith in an IDS) review the current state of tumor vaccines. Besser MJ at al., Clinical responses in a phase II study using adoptive transfer of short-term cultured tumor infiltration lymphocytes in metastatic melanoma patients, *Clin. Cancer Res.*, 16(9):2646-2655 (2010)

reported on a very good clinical response of metastatic melanoma patients to adoptive lymphocyte transfer, and Gulley et al., Immunologic and prognostic factors associated with overall survival employing a poxviral-based PSA vaccine in metastatic castrate-resistant prostate cancer, *Cancer Immunol. Immunother*, 59:663-674 (2010), review phase II clinical trails in metastatic castrate-resistant prostate cancer following a poxviral-based PSA, concluding that, although the ability to cure is marginal, it is apparent that there is increased overall survival. Perez SA et al., A new era in anticancer peptide vaccines, *Cancer*, 2071-2080 (2010), review the current state of the field to conclude that accumulating evidence has suggested that combining a peptide-based therapeutic vaccination with conventional chemotherapy can uncover the full potential of the antitumor immune response. In another review, Schreiber T.H et al., Tumor immunogenicity and responsiveness to cancer vaccine therapy: the state of the art, *Seminars in Immunology*, 22:105-112 (2010), conclude that, despite the many high-profile cancer vaccine failures over the past decade, cancer vaccines are here to stay. Relevant art thus clearly show that cancer vaccines are viable alternatives for treating cancer, and therefore the requirements set forth under 35 U.S.C. §101 have clearly been met.

Regarding some of the specific allegations raised by the examiner, applicants comment as follows:

Citing Lollini et al (2005) and Abelev et al. (1999), the examiner states on page 13 of the Office Action that the identification of tumor antigens suitable for inclusion in vaccines should require that the tumor antigen have a crucial pathogenetic role for tumor growth to avoid the selection of antigen-loss variants. Applicants however point out that this is not always true. For example, prostatic acid phosphatase, the target for the FDA approved Sipuleucel-T, is not essential for cell survival; in fact, the enzyme is of unknown molecular and physiological functions (see Zylka et al., Prostatic acid phosphatase is an ectonucleotidase and suppresses pain by Generating Adenosine, *Neuron*, 60:111-122 (2008) and Taylor-Blake and Zylka, Prostatic acid phosphatase is expressed in peptidergic and nonpeptidergic nociceptive neurons of mice and rats, *PLoS ONE*, pages 1-5 (2010), copies of which are submitted herewith in an IDS). The examiner's attention is respectfully drawn to the fact that a method causing very efficient killing of the tumor cells would leave no time for a natural selection process to even take place.

The examiner reaches the conclusion on page 14 of the Office Action that the examples:

> illustrate[s] the fact that despite the structural complexity of the fusion protein that is encoded by the claimed nucleic acid molecules, it is the at least one antigenic peptide comprising an MHC class I epitope

> that necessarily achieves the effect of stimulating immunity against the antigen, so as to prevent or treat the disease in the mammal. Thus, the issue of utility largely involves the determination of the identity of the antigen that is used to effectively immunize the mammal in order to prevent or treat the disease; the other components of the fusion protein are not as important inasmuch as, for the most part, specificity is determined by the antigenic component, and not these other components. Accordingly, antigen's identity is critical to any evaluation of the purported utility of the claimed inventions to treat any particular type of cancer. (emphasis added)

The examiner's conclusion here is incorrect and misses the point of the present invention. While it is true that the identity of the antigen may be important, it is the other components which enable the anchoring of the β2m that are the ones that provide the advantage over prior art. The crux of the present invention is a new way (mechanism) of presenting the (tumor) specific antigen, which is many times more efficient than the naturally existing mechanism used in all past attempts to produce active specific immunotherapy for cancer. The present specification at page 11 (paragraph [0033] of the published application) discloses the advantage of the present invention as follows:

> Duration of the functional MHC classI/peptide complex on the cell surface is governed by the affinity of the peptide for the MHC molecule. Dissociation of the peptide from its binding groove in the α heavy chain, results in practically irreversible

> disruption of the ternary complex formed between the α chain, β2m and peptide. Both latter components are not anchored to the cell membrane and immediately detach from the cell, while the α chain is later internalized. Stabilization of a particular class I/peptide complex by enabling fast re-association is therefore likely to result in high level of presentation of the antigenic peptide.

Thus, the crucial inventive step of the present invention lies in the anchoring of the β2-microglobulin to the antigen-presenting cell membrane. This necessitates the structural complexity of the fusion protein that is encoded by the claimed nucleic acid molecules and results in the extraordinarily efficient antigen peptide presentation.

Applicants wish to re-emphasize that it is not only the identity of the antigen that matters (when used for an indication for which it is associated with); the amount and density of antigenic peptide present on the antigen-presenting cell surface and the time it stays there is directly correlated to the cytotoxic T lymphocyte (CTL) response elicited. This is the key to the invention, because the genetically improved APCs presenting massive amounts of antigenic peptide elicit a strong CTL response in cases where traditional vaccination with peptides, relying on the natural capability of APCs to present these peptides, have failed.

Prior to the present invention, the selection of an appropriate antigen was limited by the fact that the CTL clones that would be activated by the most immunogenic peptides are probably removed by the mechanism of central tolerance, as TAA are oftentimes derived from normal rather than mutated proteins. On the other hand, less reactive antigen may not be sufficient to induce CTL priming by DC. The present invention addresses this problem. By linking the selected TAA covalently to the β2m and to the cell membrane, the present inventors were able to increase TAA avidity and enhance CTL priming by APCs. Also, as explained in the present specification at page 30, second full paragraph (paragraph [0127], last sentence of the published application) "cocktails of two or more CTL inducing peptides are employed to optimize epitope and/or MHC class I restricted coverage." Therefore, the citation of failed trials that used traditional methods of active immunization with peptides is not truly relevant to the present invention.

On another issue, the examiner alleges on page 17 of the Office Action that there are no universally accepted correlates at this time between any method of *in vitro* immune monitoring and clinical outcome and cites Wang et al., T-cell-directed cancer vaccines: the melanoma model, *Exp. Opin. Biol. Ther.*, 1(2):277-290 (2001), that *in vitro* methods, which are commonly used to assess immune post-vaccination immune response,

such as cell-mediated cytotoxicity assays, tend to "overestimate quantitatively the strength of the immune reaction within the organism (page 21 of Office Action, citing Lee et al., Increased vaccine-specific T Cell frequency after peptide-based vaccination correlates with increased susceptibility to *in* vitro stimulation but does not lead to tumor regression, *The Journal of Immunology*, 6292-6300, 1999); and that activation of peptide epitope-specific CTL is not an appropriate endpoint and a prediction or estimation of efficacy based only upon such data is imprudent or inexact (page 22, citing Gao et al., Tumor vaccination that enhances antitumor T-Cell responses does not inhibit the growth of established tumors even in combination with interleukin-12 treatment: the importance of inducing intratumoral T-cell migration, *Journal of Immunotherapy*, 23(6)643-653, 2000). On page 19 of the Office Action, the examiner further states "Whatever avenue the artisan takes, in view of the unpredictability in the art, the rarity and lack of uniformity in the successful application, and the numerous and substantial limitations encountered, the threshold of enablement is high."

It should be pointed out however that even "overestimation" of the strength of the immune reaction is useful. Applicants would further like to remind the examiner that, in addition to the *in vitro* results disclosed in the specification, applicants have previously filed a 1.132

declaration executed by Dr. Gross in response to the first Office Action on November 29, 2007, in which two experiments showing prevention and treatment of cancer in an *in vivo* animal mouse model by vaccination with a cellular vaccine of the present invention are presented.

The first experiment in the 1.132 declaration showed that mice immunized with a vaccine according to the present invention and then challenged with MO5 cells are protected from the growth of the MO5 tumors. Here, two antigenic peptides are used that are expressed by the MO5 cells; chicken ovalbumin and TRP-2181-188, a native tumor associated antigenic (TAA) peptide of the MO5 cells.

The second experiment in the declaration showed that mice challenged with MO5 cells, chicken ovalbumin-transfected variant of the spontaneous murine B16 melanoma, were successfully treated by immunization with a vaccine according to the present invention which is directed to the antigenic chicken ovalbumin peptide.

Thus, the use of the fusion protein according to the invention for treatment of cancer is supported not only by data acquired *in vitro*, but also by *in vivo* studies that clearly show the efficacy of the present invention. Accordingly, the evidence submitted clearly exceeds the high threshold of enablement.

The allegation by the examiner that animal models are not enough to show that a drug would be useful in treating cancer in humans, citing Hu, 1996; Jaeger, 1996; Mukherji, 1995; Bocchia, 2000; Gura, 1997, Lee, supra; Wang, supra; and Slinghuff, 2000, is without merit.

The Circuit Court of Patent Appeals held in *In re Langer*, 503F.2d 1380, 1393; 183 USPQ 288 (CCPA 1974) that:

> Full scale clinical trials in humans … may be necessary to establish 'commercial usefulness' in this technology. However, development of a product to the extent that it is presently commercially salable in the market place is not required to establish 'usefulness' within the meaning of §101. (emphasis added)

Moreover, MPEP 2107.03 III states:

> If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. A cursory review of cases involving therapeutic inventions where 35 U.S.C. 101 was the dispositive issue illustrates the fact that the Federal courts are not particularly receptive to rejections under 35 U.S.C. 101 based on inoperability. Most striking is the fact that in those cases where an applicant supplied a reasonable evidentiary showing supporting an asserted therapeutic utility, almost uniformly the 35 U.S.C. 101-based rejection was reversed. See, e.g., *In re Brana*, 51 F.3d 1560, 34 USPQ 1436 (Fed. Cir. 1995); *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 856,

206 USPQ 881, 883 (CCPA 1980); *In re Malachowski*, 530 F.2d 1402, 189 USPQ 432 (CCPA 1976); *In re Gaubert*, 530 F.2d 1402, 189 USPQ 432 (CCPA 1975); *In re Gazave*, 379 F.2d 973, 154 USPQ 92 (CCPA 1967); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961). Only in those cases where the applicant was unable to come forward with any relevant evidence to rebut a finding by the Office that the claimed invention was inoperative was a 35 U.S.C. 101 rejection affirmed by the court. *In re Citron*, 325 F.2d 248, 253, 139 USPQ 516, 520 (CCPA 1963) (therapeutic utility for an uncharacterized biological extract not supported or scientifically credible); *In re Buting*, 418 F.2d 540, 543, 163 USPQ 689, 690 (CCPA 1969) (record did not establish a credible basis for the assertion that the single class of compounds in question would be useful in treating disparate types of cancers); *In re Novak*, 306 F.2d 924, 134 USPQ 335 (CCPA 1962) (claimed compounds did not have capacity to effect physiological activity upon which utility claim based). Contrast, however, *In re Buting* to *In re Gardner*, 475 F.2d 1389, 177 USPQ 396 (CCPA 1973), *reh"g denied*, 480 F.2d 879 (CCPA 1973), in which the court held that utility for a genus was found to be supported through a showing of utility for one species. In no case has a Federal court required an applicant to support an asserted utility with data from human clinical trials.

If an applicant provides data, whether from *in vitro* assays or animal tests or both, to support an asserted utility, and an explanation of why that data supports the asserted utility, the Office will determine if the data and the explanation would be viewed by one skilled in the art as being reasonably predictive of the asserted utility. See, e.g., *Ex parte Maas*, 9 USPQ2d 1746 (Bd. Pat. App. & Inter. 1987); *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991). Office personnel must be careful to evaluate all factors that might

> influence the conclusions of a person of ordinary skill in the art as to this question, including the test parameters, choice of animal, relationship of the activity to the particular disorder to be treated, characteristics of the compound or composition, relative significance of the data provided and, most importantly, the explanation offered by the applicant as to why the information provided is believed to support the asserted utility. If the data supplied is consistent with the asserted utility, the Office cannot maintain a rejection under 35 U.S.C. 101. (emphasis added)

Based on the knowledge and skill of those in the art and the guidance and teachings in the specification, i.e., enhanced presentation of MHC Class I epitope from a TAA, and examples of TAA peptides associated with particular cancers/tumors (see pages 15-17 of the present specification), it would be credible to those of skill in the art that the enhanced presentation of a TAA would be useful in treating the cancer/tumor with which the TAA is associated.

On page 23, the examiner turns his attention to vaccines comprised of nucleic acid molecules. Claims 37-39, directed to a DNA vaccine, and claims 49-51, directed to a pharmaceutical composition comprising as active ingredient at least one polynucleotide of claim 1, are now cancelled without prejudice, thereby obviating the rejection with regard to these claims.

In view of the discussion above and the amended set of claims, the presently claimed invention is clearly supported by a

specific and substantial asserted utility as well as by a well-established utility.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1, 3, 5, 11-44, 47-53, 56, and 57 have also been rejected under 35 U.S.C. 112, first paragraph, because the examiner states that, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The examiner recites the Wands factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". On page 28 of the Office Action, the examiner states:

> Moreover, it is apparent that the amount of guidance, direction, and exemplification disclosed in the specification is not reasonably commensurate in scope with the claims; and in fact, it is duly noted that there are no disclosures in this application pertaining to any exemplifying experiments or studies to show that the claimed inventions can be used as intended to prevent or treat cancer or infectious disease. The specification would at best only reasonably permit the claimed products to be made, but not used without undue experimentation.

This rejection is respectfully traversed.

As explained and argued above with regard to the §101 utility rejection, this is not true. Both the teachings in the specification and the executed 1.132 declaration of Dr. Gross previously made of record provide ample guidance, direction, and exemplification that is clearly commensurate in scope with the present claims.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1, 3, 5, 11-31, 38, 39, 49-51, and 53 have been rejected under 35 U.S.C.112, second paragraph, as being indefinite. This rejection is respectfully traversed.

(a) The examiner states that claim 1, for example, is directed to a polypeptide that is capable of "high level presentation of antigenic peptides on antigen-presenting cells," but yet it cannot be ascertained relative to what standard of comparison a determination of the level of presentation of antigenic peptides by the APCs must be made so as to know whether or not the level is considered "high".

As taught in the present specification at page 35 (paragraph [0144] in the published application),

> Quantitative analysis of antigen level on the surface of both transfectants and parental MD45 cells is shown in Table 2 and reveals occupation of 20% of surface H- Kk molecules of 427-24 cells by the Ha255-262 peptide… Also noteworthy is the 3-fold increase in the total amount of H-2K^{k} in both transfectants

425-44 and 427-24, compared with the parental MD45 cells.

The legend of Table 2 teaches the assay used to measure peptide antigen level on the surface of cells. A similar experiment, assessing surface expression of antigenic Kb/OVA257-264 complex in RMA-S cells transfected with OVA257-264 fused to membranal β2m, revealed 57% H-2Kb occupancy in the transfectant (specification page 40, last paragraph; paragraph [0173] of published application).

Furthermore, in the first full paragraph on page 42 of the present specification (paragraph [0178] of published application), an experiment is described in which a stable transfectant, designated D323-4, which expresses a high level of hβ2m (not linked to an antigenic peptide, and thus free to bind exogenously added peptide), was assessed for peptide presentation. In this experiment the inventors evaluated the ability of the transfectant to bind exogenously added synthetic OVA257-264 peptide through H-2Kb, in comparison with parental RMA-S cells, exploiting the complex-specific 25D-1.16 mAb. This experiment was repeated 6 times, producing essentially identical results. The results demonstrate approximately a 3 log enhancement of the ability to bind exogenous peptide, while maximal level of binding increases only 3-4-fold compared with RMA-S cells. These findings imply that expression of the β2m

products results in a vast enhancement in the functional affinity of the antigenic peptide to the MHC class I molecule. It should be noted that the nature of the β2m anchor (CD3 ζ in KD21-6 or H-2Kb in D323-4) has little influence on the magnitude of this striking phenomenon.

The above experiment shows that the amount of polypeptide capable of peptide presentation expressed on the cell surface is 3-4 fold higher than in the control cells, but the functional affinity of the polypeptide to the peptide is about a thousand times higher, i.e., the peptide is presented at both a higher amount and for longer periods of time. This is because the wild type β2m is not bound to the cell membrane and when the peptide leaves the MHC I complex, β2m is released from the cell surface and the α-chain is internalized, thus enabling only a short time of presentation of the peptide. The β2m construct of the present invention, on the other hand, is bound to the membrane and thus, the MHC-I-peptide complex is much more stable. It should also be appreciated that in the natural setting, an APC presents about 10^5 to 10^6 MHC molecules on its surface, and each one of the many thousands of antigenic peptides displayed is bound and displayed by as few as about 10-100 MHC complexes per cell, i.e., an occupancy of 0.001-0.1%. As shown in the Examples of the present specification, the expression of the polypeptide

according to the invention in an APC results in about 50% occupancy or higher.

Thus, the present specification clearly discloses the meaning of "high level presentation of antigenic peptides on antigen-presenting cells": The first parameter is the level of expression which is 3-4 fold higher than in wild type APCs; the second parameter is the functional affinity with about 1000 times higher than in wild type APCs; and the third parameter is the occupancy that is about 50% in APCs transfected with the polypeptide according to the present invention as compared with maximum 0.01% in wild type APCs. The specification also teaches methods readily available to the ordinary artisan for measuring these parameters.

The Court of Appeals, Fifth Circuit, held in *Arnold Pipe Rentals Company, Inc. v. Engineering Enterprises*, 146 USPQ 421, that:

> Absolute precision in the wording of claims, while desirable, would be an unreasonable burden to impose on an inventor. Descriptive words such as "substantial", "high", "about," and "slight excess" have often withstood attack under §112. (emphasis added)

The Court of Appeals, District of Columbia, later similarly held in *Charvat v. Commission of Patents*, 182 USPQ 587, that:

> Our conclusion assumes, of course, that the phrase "on the order of: would trigger some recognition in a person of ordinary skill in

> the grinding art, perhaps delineating, at a minimum, heavy-duty grinding wheels from polishing wheels. As for the other relative phrases—such as "high concentration," and particles that are "slightly spread apart"—it seems certain to us that such a person would not fail to distinguish the claimed wheel from Tocci-Guilbert when he reads the detailed figures and descriptions in the specifications, as well as the description of the preferred method of manufacture. Even if broadly construed, these relative expressions describe a grinding wheel which is fundamentally different in structure from Tocci-Guilbert as our earlier analysis demonstrates. (emphasis added)

For the reasons discussed immediately above, the recitation of "high level presentation of antigenic peptides on antigen-presenting cells" is not indefinite.

(b) The examiner holds that claims 14 and 23 recite the limitation "said antigen", which in both cases does not find antecedent basis in the language of the preceding claims, and therefore, it cannot be ascertained to which antigens the claims are directed.

Claims 14 and 23 refer to claim 12, which recites "…one sole antigen." Thus, both claims find antecedent basis in the language of the preceding claim. Nevertheless, this part of the rejection is made moot by the cancellation of claims 14 and 23 without prejudice.

(c) The examiner holds that claim 53 is indefinite because the claim recites the limitation "the antigen", but the

preceding claim is directed to more than one antigen and it is not clear to which antigen claim 53 refers.

Claim 53 is now cancelled without prejudice, and this rejection is therefore moot.

(d) The examiner holds that claims 1, 3, 5, 11-31, 38, 39, 49-51, and 53 are considered indefinite because the claims use designations such as "CD40", "MAGE" and "gp100" as the sole means of identifying the polypeptides or antigens to which the claims refer. The examiner states that use of laboratory designations only to identify a particular polypeptide or a family of polypeptides renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct polypeptides. For example, according to the examiner the terms "MAGE" and "BAGE" do not identify a single particular polypeptide but rather a family of structurally and functionally disparate family members, and although some members of a given family may be associated with cancer (e.g., are overexpressed by cancer cells relative to normal cells of the corresponding tissue or organ), other members are not. The examiner cites De Plaen et al. (1994), who teach that six of the members of the MAGE gene family were found to be expressed at a high level in a number of tumors of various histological types; while five were very weakly expressed in all

samples tested, and one, namely MAGE 7, was not transcribed at all in the ninety-five tumor samples tested.

A skilled artisan who intended to implement the invention for the purpose of making a cancer vaccine would not consider using antigen isoforms that are not TAAs because it would not serve his purpose. For example, there is no need to define that MAGE 7 is not included, because the skilled artisan, knowing that it is not associated with cancer, would not consider including it in the polypeptide of the invention. See the specific examples of TAA peptides associated with specific types of cancers on pages 15-17 of the present specification. Therefore, the polypeptides to which the claims are directed are clearly and unambiguously identified to the skilled artisan.

The examiner has also rejected the term "CD40", because it identifies not just one particular polypeptide, but rather any of a number of orthologs encoded by genes in different mammals. The same is true of the term "human CD3 ζ polypeptide", which has been described as having a number of structurally and functionally disparate isoforms. The examiner cites Tsuzaka et al. (2006) and Atkinson et al. (2003), to argue that mRNA slice variants encoding variant forms of CD3 ζ polypeptides exist.

The role of the CD40 and CD3 ζ polypeptides in the polypeptide of the present invention is to anchor the β2m to the cell membrane. This function is performed very well by as

disparate polypeptides as CD40, HLA and CD3 as shown in the present specification in Examples 1 to 5. For instance, Example 5 demonstrated that a fusion polypeptide comprising the CD40 transmembrane and cytoplasmic portions successfully anchored the polypeptide to the cell membrane. Since polypeptides as disparate as CD40, HLA and CD3 are shown in the present specification to be capable of exerting the same function of anchoring the polypeptide to the cell membrane, there can be little doubt that any other transmembrane polypeptide with a cytoplasmic tail could fill the same function, as well as undoubtedly polypeptides closely related to CD40 or CD3 as the orthologs and isoforms discussed in the Office Action. Therefore, the claims define the metes and bounds of the subject matter that is regarded as the invention (in this case "a polypeptide which can exert the required anchoring function") with sufficient clarity and therefore permit the skilled artisan to know or determine infringing subject matter.

(e) The examiner holds that claim 19 is indefinite because the claim recites the HLA-2 binding peptide derived from gp100 and the gp100 HLA-A3 binding peptide are selected from the group consisting of the amino acid sequences identified by the claims, but it cannot be ascertained if the claimed peptides comprise or consist of any of these amino acid sequences. This part of the rejection is obviated by the amendment to claim 19.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1, 3, 5, 11-44, 47-53, 56, and 57 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This rejection is respectfully traversed.

The examiner is of the opinion that the whole transmembrane domain is required to span the membrane and to anchor the polypeptide and that the claimed partial domain is not well defined. Applicants thank the examiner for drawing their attention to this inaccuracy, and the claims are amended accordingly to now recite "…a polypeptide which can exert the required anchoring function, consisting of the full transmembrane domain and full or partial cytoplasmic domain of a molecule…" This part of the rejection is now believed to be moot.

Turning to a different issue, the examiner alleges that the claims are directed to a genus that cannot be said to be adequately represented by those peptides that are particularly described by the specification. This is in part because the peptide need only be derived from any of the aforementioned antigens, the structure of the peptide of which the fusion polypeptide encoded by the claimed polynucleotide need not have any particular structure. According to the examiner, the claims are directed to antigenic peptides that are defined by their

immunogenic properties alone; yet, a generic statement that defines a genus of substances by only their functional activity, i.e., the ability to stimulate a specific immune response in a mammal, does not provide an adequate written description of the genus.

Applicants respectfully disagree. First of all, as applicants have discussed above, it is again re-emphasized that the invention does not lie in the discovery of TAA peptides, numerous examples of which were previously discovered by others and are well known in the art; rather, it lies in the enhanced presentation of antigenic peptides on antigen-presenting cells conferred by the polypeptide (encoded by the polynucleotide construct) in stably anchoring the peptide to the membrane of an APC. Many TAA peptides associated with different cancers/tumors are well known in the art. A representative number of such TAA peptides are described on pages 15-18 of the present specification. Indeed, the number of TAA peptides specifically disclosed on pages 15-18 total at least 34 different peptides and is clearly sufficiently "representative" of the genus, as would certainly be recognized by those of skill in the art.

Secondly, it should also be pointed out that, insofar as the claims to polynucleotide and antigen-presenting cells are concerned, since there is no recitation of function of the TAA and the claims are not method claims requiring such a function,

the fact that many TAA peptides are well known in the art and the fact that the present specification lists a "representative" number of at least 34 TAA peptides associated with cancers/tumors is sufficient to satisfy the written description requirement.

Furthermore, regarding the specific issues raised by the examiner in this rejection, as mentioned above, the specification discloses specific activation of B3Z, an H-2K^{b}-restricted, OVA$_{257-264}$-specific CTL hybridoma, by RMA-S clones expressing dcβ_2m with OVA$_{257-264}$ (Example 2, paragraph [0174] of the published application), and of CTLs prepared from mice immunized with RMA-S cells expressing OVA$_{257-264}$ linked to β2m (Example 4, paragraph [0179] of the published application).

In addition, applicants refer to the data submitted with the executed 1.132 declaration submitted in response to the first Office Action. Mice were challenged with MO5 cells, which express both chicken OVA as a xenoantigen, providing the immunodominant H-2K^{b}-binding OVA$_{257-264}$ peptide and TRP-2, a self-melanocyte differentiation Ag, harboring the poorly immunogenic peptide TRP-2$_{181-188}$, which binds H-2K^{b} with low affinity. The mice were immunized with RMA-S cells expressing either a TRP-2$_{181-188}$-bearing construct or a OVA$_{257-264}$-bearing construct. Preventive and therapeutic efficiency was evident in mice immunized with either of the two antigens.

The examiner further notes that any given polypeptide may or may not be immunogenic in a mammal, as many polypeptides fail to induce an immune response because the mammal's immune response is tolerant to the polypeptide. The examiner cites Khong et al. (2002) using traditional active immunization with antigenic peptide, to argue that despite the ability to predict which peptides are capable of binding MHC class I molecules, the skilled artisan cannot reliably predict which of such peptides are capable of stimulating cytotoxic T cells directed against a tumor associated antigen, such as TRP2-6b or any other antigen associated with a disease.

The examiner also expresses his concerns that inasmuch as the claims are directed to a genus of structurally disparate antigenic peptides that are derived from tumor associated antigens, for example, it is aptly noted that since their structures may vary substantially many may not elicit an immune response directed against the antigen from which they were originally derived. Then, too, only certain immunogenic fragments might be expected to effectively induce antigen-specific cytotoxic T lymphocytes (CTL) that will kill the cancer cells; other immunogenic fragments will not be effective. This position is held to be supported, for example, by the teachings of Lu et al. (Cancer Research 2002; 62: 5807-5812), where Lu et al. is said to teach that four of five immunogenic fragments of the

prostate cancer-associated antigen PSMA were capable of inducing antigen-specific CTL killing of target cells, but only one was effective at recognizing prostate tumor cells expressing the protein; see the entire document (e.g., the abstract). Thus, according to the examiner, while some immunogenic fragments of any given tumor-associated antigen may effective to stimulate a CTL-mediated response to the immunogenic fragment, it seems that the artisan cannot predict which immunogenic fragments might be used to elicit an effective anti-tumor immune response, which prevents or suppresses the onset, growth, and/or malignant progression of the disease.

With due respect to the examiner, the exceptionally high efficiency of antigen presentation in antigen presenting cells expressing the polypeptides of the present invention makes the comparison with cellular vaccines disclosed in the documents cited by the examiner irrelevant since those vaccines are inherently inferior to those of the present invention, especially in view of the new results presented in the executed Gross 1.132 declaration of record. As explained above, by linking the selected TAA covalently to the β2m and to the cell membrane, the inventors were able to increase TAA avidity by a 1000-fold and enhance CTL priming by APCs. Thus, even weakly antigenic peptides presented according to the present invention, for example TRP-2 used in the experiment submitted in the 1.132

declaration, are capable of eliciting CTL response and tumor disseminating activity. Again, to re-emphasize, since the polypeptide of the present invention confers superior antigen presenting capability as compared with prior art, comparison with the results disclosed in the cited documents is futile.

Moreover, regarding the issue of structure-function correlation, the Court of Appeals for the Federal Circuit held in *Enzo Biochem v. Gen-Probe*, 323 F.3d 956:

> It is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement. The PTO has issued Guidelines governing its internal practice for addressing that issue. The Guidelines, like the Manual of Patent Examining Procedure ("MPEP"), are not binding on this court, but may be given judicial notice to the extent they do not conflict with the statute. See *Molins PLC v. Textron, Inc., 48 F.3d 1172, 1180 n.10, 33 USPQ2d 1823, 1828 n.10 (Fed. Cir. 1995)*. In its Guidelines, the PTO has determined that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106 (emphasis added). For example, the PTO would find compliance with *§ 112*, P 1, for a claim to an "isolated antibody capable of binding to [**16] antigen X," notwithstanding the functional definition of the antibody, in light of "the well defined structural characteristics for the five classes of antibody, the functional

> characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/patents/guides.htm ("Application of Guidelines"). Thus, under the Guidelines, the written description requirement would be met for all of the claims of the '659 patent if the functional characteristic of preferential binding to N. gonorrhoeae over N. meningitidis were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed. We are persuaded by the Guidelines on this point and adopt the PTO's applicable standard for determining compliance with the written description requirement. (emphasis added)

The knowledge about MHC/peptide complexes, the interaction with T cell receptors (TCRs), and their structure-function correlation is at least as broad and deep as the knowledge about antibodies and their structure-function correlation with antigens.

Analogous to what the USPTO found to be in compliance with the written description requirement for antibody binding to antigen, the review articles of Pamer and Cresswell, Mechanisms of MHC Class I-Restricted Antigen Processing, *Annu. Rev. Immunol.* 16:323-258 (1998) and Marrack et al., Evolutionarily conserved amino acids that control TCR-MHC interaction, *Annu. Rev. Immunol.* 26:171-203 (2008), copies of which are submitted herewith in an IDS, are representative of what was known about MHC class I-peptide and TCR structure and interaction corresponding to the "defined structural characteristics for the five classes of

antibody" and "functional characteristics of antibody binding", as held in the highlighted *Enzo* decision above, at the time the invention was made (even though the review article of Marrack et al. was published in 2008, much about TCR structure and TCR-MHC interactions reviewed therein was known at the time the present invention was made).

For instance, with regard to the structure of the MHC-peptide, the Pamer and Cresswell (1998) article teach in the paragraph bridging pages 323 to 324 that:

> MHC class I molecules are expressed on the surface of virtually all nucleated cells, where they serve as the target antigens for CD8- positive T cells. They consist of a membrane-integrated glycoprotein, which is the polymorphic product of one of the MHC class I genes, a small soluble protein, β2 microglobulin (β2m), and a short peptide usually of 8–10 amino. Numerous examples of class I–peptide complexes have been successfully crystallized and their three-dimensional structures determined (1). The characteristic feature of the molecule is the peptide binding site, which consists of two antiparallel α-helices overlaying a platform of antiparallel α-strands. The peptide lies in the groove so formed, with its N- and C-termini and a subset of its amino acid side chains interacting with the binding groove to produce an extremely stable, high-affinity interaction. (emphasis added)

With regard to TCR structure and TCR-MHC interaction, Marrack et al. (2008) teach at the bottom of the right column on page 172 to the end of the first full paragraph on page 173 (see also Fig. 1) that:

> TCRs are now known to comprise two chains, α and β, each composed of variable (Vα, Nα, Jα; Vβ, Dβ, Nβ, Jβ) and constant elements with all but the N regions encoded by the germ line (21). Biochemical, cellular immunological, and later, crystallography experiments showed that TCRs react usually with a complicated ligand composed of the α helices of MHC proteins and peptides derived from antigen, bound to specially designed grooves of MHC molecules (22-26). Investigators have reported a number of structures of TCRs bound to their MHC/peptide ligands (27-46). TCRs bind MHC/peptide via their complementarity determining region (CDR) loops: CDR1α, CDR2α, CDR1β, and CDR2β, encoded in the germ line, and CDR3α and CDR3β, made up at least partially of non-germ line encoded residues and the C-terminal and N-terminal ends of Vα or Vβ and Jα or Dβ/Jβ, respectively. In these structures, the TCRs often lie on a diagonal above the face of MHC/peptide (Figure 1). The six CDR loops of TCRs contact this face, to varying degrees, usually with CDR1α and CDR2α over the α2 helix of MHC class I (MHCI) or the β helix of MHC class II(MHCII), and CDR1β and CDR2β over the α1 helix of MHCI or the α helix of MHCII. Conversely, the interactions of CDR3α and CDR3β usually focus on amino acids of the peptide. (emphasis added)

Marrack et al. further teach on page 174, last paragraph through page 175, first full paragraph, that:

> TCRs usually bind MHC/peptide in approximately the same orientation (as mentioned above): angled across the MHC α-helices with the TCR α chain over the α2 helix of MHCI or the β helix of MHCII, and the TCR β chain CDR regions over the MHC helices α1/α (reviewed in References 65 and 66) (Figure 1)...
>
> …the pivot point of the TCR on MHC is usually in approximately the same location:

> centered over peptide amino acids 4-6 in MHCI and peptide amino acid 5 (P5) in MHCII complexes.

It should be pointed out that, from the knowledge in the art, the peptide's (e.g., TAA peptide) interaction with the MHC or TCR is defined only by its length and the amino acid position that is involved in an interaction, not its sequence.

As for the portion of the highlighted *Enzo* decision above relating to "the fact that the antibody technology is well developed and mature", applicants cite Matsui et al., Kinetics of T-cell receptor binding to peptide/I-E^k complexes: Correlation of the dissociation rate with T-cell responsiveness, *Proc. Natl. Acad. Sci. USA* 91:12862-12866 (1994), a copy of which is also submitted herewith in an IDS, which disclose that the authors have prepared soluble TCRs and used it to measure TCR/MHC-peptide binding kinetics. This also gives information analogous to "characteristics of antibody binding". The authors are not the first to develop soluble TCRs as they cite the 1992 article of Weber et al., and the applicants advise that soluble TCRs are commercially available. On page 12865, last paragraph, Matsui et al. discuss their findings, i.e., the kinetics of TCR ligand interactions:

> With respect to kinetic parameters, we find that TCR ligand interactions examined here have very slow association rates (900-3000 M-1 s-1 for the various MCC peptide/I-Ek complexes and the 2B4 TCR) and very fast off-rates (0.30-0.06 s-1). These slow

> association rates indicate that the binding of the TCR to its ligand is in some way intrinsically limited. One explanation is that it is dependent on a conformational change in either the MHC molecule (25) or the TCR (26) or both. A related hypothesis would be that the peptide side chains which have to bind to the TCR must be oriented in a specific way. The rapid dissociation rates indicate that any single interaction will have a tl/2 << 1 min. Additionally, we find that the dissociation rate may have a dominant effect on the T-cell stimulatory ability of a given peptide/MHC complex, at least within the very narrow affinity range that we find in this system.

Accordingly, structure-function correlation between MHC Class I and peptides, such as TAA peptides, and TCR were well known and established at the time the present invention was made, and TAA peptides were predicted to bind to MHC Class I molecules using computer algorithms based on such structure-function correlations.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1, 3, 11, 12, 23, 24, 26, 29-32, 34, 36, 37, 39, 40, 49, 51, and 52 have been rejected under 35 U.S.C. 102(b) as being anticipated by WO0101698. The examiner states that the antigenic peptide related to an autoimmune disease of WO0101698 is the same as the antigenic peptide of the fusion protein encoded by the claimed polynucleotide, which is "at least one idiotypic peptide expressed by autoreactive T lymphocytes". This rejection is obviated by the amendments to the claims, which

include deletion of the recitation "at least one idiotypic peptide expressed by autoreactive T lymphocytes" without prejudice.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1, 3, 11-13, 26, 29-33, 34, 37, 40, 49, and 52 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1- 16 of U.S. Patent No. 7,319,143. The examiner states that:

> Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons: Claims 1-16 of the patent are directed to a DNA molecule encoding a fusion polypeptide comprising a β2-microglobulin molecule adjoined to a peptide, which in turn is adjoined to a fragment of the human CD3 ζ polypeptide comprising its transmembrane and cytoplasmic domains, wherein the β2-microglobulin molecule is also adjoined to another peptide, which is antigenic and related to an autoimmune disease. Although the claims of the patent are not expressly directed to an antigenic peptide that comprises a MHC class I epitope of any of a tumor-associated antigen, an antigen from a pathogen, or an idiotypic peptide expressed by autoreactive T cells, the peptide is antigenic and is related to an autoimmune disease. Accordingly, it seems that the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the patent anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the patent.

Applicant disagrees with the examiner on the grounds that the fact that the expression of the construct in a T-cell leads to efficient presentation of antigenic peptide, coupled with the activation of the T-cell that leads to the effective destruction of autoreactive T-cells, does not necessarily mean that the expression of the construct in an APC would lead to efficient presentation of the antigenic peptide on the APC and subsequent activation of T-cells. Applicants again emphasize that the identity of the antigen is not the central issue; rather, it is the efficient display of the antigen on the surface of the APC, and there is no hint or suggestion in U.S. Patent 7,319,143 that would motivate the ordinary skilled artisan to express the construct of US 7,319,143, or one with another antigenic peptide, in an APC.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1, 3, 11-24, 26, 29-44, 47-53, 56, and 57 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 6-25 of copending application no. 11/541,566. The examiner holds that, although the conflicting claims are not identical, they are not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not yet been

patented. Applicants request that this provisional rejection be either held in abeyance until such time that the conflicting claims of copending application no. 11/541,566 are patented before the claims of the present application or withdrawn when there are any allowed claims in the present application that will become patented before the conflicting claims of the copending application.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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